Exhibit 5

REVIEW

Psychiatric Adverse Effects of Corticosteroids

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Psychiatric adverse effects during systemic corticosteroid therapy are common. Two large meta-analyses found that severe reactions occurred in nearly 6% of patients, and mild to moderate reactions occurred in about 28%. Although disturbances of mood, cognition, sleep, and behavior as well as frank delirium or even psychosis are possible, the most common adverse effects of short-term corticosteroid therapy are euphoria and hypomania. Conversely, long-term therapy tends to induce depressive symptoms. Dosage is directly related to the incidence of adverse effects but is not related to the timing, severity, or duration of these effects. Neither the presence nor the absence of previous reactions predicts adverse responses to subsequent courses of corticosteroids. Corticosteroid-induced symptoms frequently present early in a treatment cycle and typically resolve with dosage reduction or discontinuation of corticosteroids. In severe cases or situations in which the dose cannot be reduced, antipsychotics or mood stabilizers may be required. This review offers an approach to identifying and managing corticosteroid-induced psychiatric syndromes based on the type of symptoms and anticipated duration of corticosteroid treatment.

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HPA = hypothalamic-pituitary-adrenal axis; SSRI = selective serotonin reuptake inhibitor

Since Edward Kendall isolated cortisone in the late 1930s and Philip Hench first used it to treat rheumatoid arthritis in 1948, both events occurring at the Mayo Clinic in Rochester, Minn, corticosteroids have become the cornerstone of therapy for many neurologic, respiratory, gastrointestinal, renal, endocrine, hematologic, neoplastic, rheumatologic, dermatologic, ophthalmic, and allergic conditions. More than 10 million new corticosteroid prescriptions are filled each year,[1] with up to 0.9% of the general population[2] and as many as 7% of hospitalized patients[3] receiving oral corticosteroid therapy at any given point. Corticosteroids are used to treat both acute (eg, asthma exacerbation) and chronic (eg, systemic lupus erythematosus) conditions. Management strategies differ substantially depending on the underlying disease.

Although a powerful therapeutic option, corticosteroids are associated with serious adverse effects, both physiologic and psychiatric. While the somatic adverse effects of corticosteroid therapy (Table 1) have been extensively researched and widely described, the neuropsychiatric adverse effects have received less attention. Moreover, the etiology and pathogenesis of these brain effects remain poorly understood. The neuropsychiatric adverse effects of corticosteroids are complex, unpredictable, and often severe, ranging across most categories of psychopathology.[4] Mood lability, anxiety symptoms, cognitive impairments, behavioral disturbances, or psychotic features can present alone or in combination. Further complicating our understanding of corticosteroid-induced adverse effects are the ill-defined diagnoses and vague clinical descriptors given to symptom complexes and syndromes in the early literature on this topic. From this tradition comes the term *steroid psychosis*, which describes a variety of distinct conditions, not all of them psychotic, that are linked only through their inciting etiology.

Our objective in this review was to offer an approach to identifying and managing corticosteroid-induced psychiatric syndromes based on the type of symptoms and anticipated duration of corticosteroid treatment. Toward that end, the PubMed database was searched using the following key words alone or in combination: *steroid psychosis*, *steroid reaction*, *corticosteroid*, *glucocorticoid*, *cortisol*, *psychiatric*, *psychotic*, *affective*, and *depression*. Bibliographies of identified articles were then searched for additional references, as were bibliographies of standard psychiatry, endocrinology, and internal medicine texts in the Mayo Clinic library collection that included references to corticosteroid therapy and steroid psychosis. Data from identified articles were included based on the authors' judgments as to whether they furthered the goal of synthesizing known information about corticosteroid psychiatric adverse effects.

ADVERSE EFFECTS

Psychiatric Disturbances

Long-discounted mid 20th-century studies by Rome and Braceland[5] and Garner and Falk[6] suggested that the occurrence of corticosteroid-induced psychiatric reactions depended on the patient's premorbid personality organizations. Brody[7] also suggested that these reactions reflected an extreme version of a patient's usual stress reaction. More

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TABLE 1. **Adverse Somatic Effects of Corticosteroid Therapy**

Cardiovascular
Hypertension
Accelerated atherosclerosis
Dermatologic
Acne
Alopecia
Hirsutism
Striae
Skin atrophy
Purpura
Endocrine
Obesity
Diabetes mellitus
Adrenal-pituitary axis suppression
Hyperlipidemia
Fluid and sodium retention
Loss of potassium, calcium, and nitrogen
Delayed growth
Gastrointestinal
Peptic ulcer disease
Pancreatitis
Fatty liver
Hematologic
Leukocytosis
Neutrophilia
Lymphopenia
Infectious
Oral candidiasis
Increased risk of systemic infection
Musculoskeletal
Myopathy
Osteoporosis
Avascular necrosis
Neurologic
Pseudotumor cerebri
Ophthalmologic
Cataracts
Glaucoma

Adapted from Keenan G. Management of complications of glucocorticoid therapy. *Clin Chest Med*. 1997;18:507-520, with permission from Elsevier.

recent studies show that corticosteroids universally induce central nervous system effects, some dramatic enough to attract clinical attention. In our literature review, we found that the potential psychiatric adverse effects of corticosteroids span a symptom spectrum from subtle mood changes to full-blown affective syndromes and frank psychosis.

In this article, we define clinically significant symptoms as those that disrupt patients' daily lives or cause duress to them or those around them. We characterize mild to moderate reactions as those representing changes in mood or behavior that do not reach the level of a diagnosable psychiatric disorder. The most frequently identified symptoms include agitation, anxiety, distractibility, fear, hypomania, indifference, insomnia, irritability, lethargy, labile mood, pressured speech, restlessness, and tearfulness. Following the lead of Smyllie and Connolly,[8] who in 1968 defined a severe reaction as "serious enough to require psychiatric advice and treatment," we define a severe reaction as a constellation of major symptoms consistent with a diagnosable affective syndrome, psychotic disorder, delirium, or another psychiatric condition. The most commonly reported corticosteroid-induced psychiatric disturbances are affective, including mania, depression, or mixed states. Most often, patients receiving short-term corticosteroid therapy present with euphoria or hypomania, whereas long-term therapy tends to engender depressive symptoms.[9] Although mood disorders occur in the vast majority of cases, either delirium or frank psychosis, typified by hallucinations, delusions, and disorganized thought, is the presenting syndrome in a sixth of patients.[10-12] Severe episodes of depression, mania, or psychosis frequently include suicidal ideation.

Cognitive Deficits

Cognitive deficits, particularly declarative or verbal memory deficits, have been well documented during both long- and short-term corticosteroid therapy. Deficits during short-term therapy are consistent with hippocampal dysfunction and occur with reversible atrophy of hippocampal neurons.[13-15] New declarative memory deficiencies may emerge after only 4 to 5 days of dexamethasone or prednisone therapy.[16] These disturbances appear to be dose dependent and reversible with corticosteroid discontinuation.

More severe cognitive impairment consistent with delirium or dementia has also been described.[17,18] In a review of corticosteroid psychoses, Hall et al[19] identified marked distractibility in 79% of cases and intermittent memory impairment in 71%. Persistent memory impairment in 7% suggested corticosteroid-induced dementia. Proposed explanations for persistent cognitive impairment focus on increased hippocampal vulnerability to irreversible damage via several mechanisms.[20]

INCIDENCE

Studies reporting the incidence of corticosteroid-associated adverse psychiatric reactions have cited rates ranging from 1.8% to 57% of patients. The substantial variability in reported incidence reflects the unpredictability of these reactions, the large variations in researchers' definitions of reactions, the wide range of doses, and the diverse patient groups.

In a meta-analysis of 11 uncontrolled studies involving 935 adult patients, Lewis and Smith[11] found incidences of psychiatric reactions ranging from 13% to 62% with a weighted-average incidence of 27.6%. Most of these reactions were considered mild or moderate on a 3-point scale (mild, moderate, severe). In the same article, the authors also provided a best estimate of severe corticosteroid-in-

TABLE 2. **Corticosteroid Dose Equivalency**

Corticosteroid	Glucocorticoid activity	Half-life (h)	Equivalent dose (mg)	Equivalent dose (mg)	Equivalent dose (mg)
Cortisol (hydrocortisone)	1	8-12	20	160	320
Cortisone	0.8	8-12	25	200	400
Prednisolone	4	18-36	5	40	80
Prednisone	4	18-36	5	40	80
Methylprednisolone	5	18-36	4	32	64
Dexamethasone	25	36-54	0.8	6.4	12.8

duced psychiatric disturbances.[11] In their meta-analysis of 2555 patients from 13 uncontrolled studies that evaluated the efficacy of corticosteroids for treatment of various medical illnesses, the weighted-average incidence of severe psychiatric disturbances was 5.7%.

In a study conducted by Naber et al,[21] 50 ophthalmologic patients, previously free of psychiatric symptoms, received high-dose methylprednisolone or fluocortolone (mean starting dose, 119±41 mg/d gradually tapered to 75±22 mg/d) for 8 days. Of these 50 patients, 26% (13/50) developed mania, and 10% (5/50) developed depression, all within 3 days of initiation of therapy. Likewise, in a prospective, double-blind crossover study of 12 healthy volunteers receiving 80 mg of prednisone or placebo for 5 days, Wolkowitz et al[22] found that 75% (9/12) self-reported behavioral changes during the prednisone administration period. Eight subjects described symptoms suggestive of mild hypomania and 1 of depression.

In a case-control study of 20 patients receiving long-term low-dose corticosteroid therapy (prednisone, 7.5 mg/d for >6 months) and 14 volunteers with similar illnesses who were not receiving corticosteroid therapy, Bolanos et al[9] found a 60% lifetime risk of corticosteroid-induced mood or anxiety disorder. These patients presented more commonly with depression than with mania, a characteristic difference associated with long-term corticosteroid therapy. These findings are consistent with published reports of patients with Cushing disease, a disorder of excessive endogenous cortisol production, in which depression was identified in 67% of patients,[23] whereas mania was identified in only 27% to 31%.[24]

Few substantive studies have focused on children's responses to corticosteroids. In case series of children with such discrete conditions as asthma and nephrotic syndrome, up to 50% of those receiving oral glucocorticoids have had adverse behavioral and affective effects.[25] Much like adults, children receiving corticosteroid therapy have exhibited elevated levels of depression and anxiety,[26] as well as increases in insomnia, tearfulness, irritability, argumentativeness, fatigue, aggression, and inattentiveness.[27] In a recent literature review,[28] 16 case reports of severe "adverse psychological effects including psychotic effects" were identified.

A small group of patients have recurrent psychiatric reactions to corticosteroids. Little research has been conducted in this subset of patients. Wada et al[29] described 9 patients with recurrent symptoms and reviewed the literature for insight into this population. They found that patients with recurrent corticosteroid-induced mood disorders had a high prevalence of psychotic features, with 6 of 9 patients developing psychotic features that complicated depressive, manic, or mixed affective states.

RISK FACTORS

The corticosteroid dosage is the most important risk factor for the development of psychiatric symptoms. Hydrocortisone equivalents for 6 commonly prescribed corticosteroids are shown in Table 2. The Boston Collaborative Drug Surveillance Program[3] monitored 676 consecutive hospitalized patients who received prednisone therapy and recorded a 1.3% (6/463) incidence of psychiatric disturbances in patients receiving 40 mg/d or less, a 4.6% (8/175) incidence in patients receiving 41 to 80 mg/d, and an 18.4% (7/38) incidence in patients receiving more than 80 mg/d. Interestingly, dose does not predict onset, severity, type, or duration of symptoms.[30,31] Neither previous corticosteroid-induced psychiatric disturbances nor previous treatment(s) free of such disturbances predicts future responses to treatment. Likewise, a history of psychiatric illness does not predict occurrence.[32] No particular age group appears to be at increased risk,[11,12] although sex seems to be a factor. Females have a minimally, but statistically significant, increased risk of psychiatric disturbances. This is true even after correcting for the higher proportion of women with medical conditions who require substantial corticosteroid doses.[12]

TIMING OF ADVERSE REACTIONS

Psychiatric disturbances can occur at any point during corticosteroid treatment, including almost immediately after

initiation and even after cessation of treatment. However, most occur early in the therapeutic course. In a prospective case series of 14 patients, Hall et al[19] found that 86% (12/14) of patients developed psychiatric adverse effects within the first week of treatment. In a review of 70 case reports, Lewis and Smith[11] found a median time to onset of 11.5 days, with 39% of disturbances occurring during the first week, 62% within 2 weeks, and 83% within 6 weeks of treatment initiation.

CORTICOSTEROID ABUSE

Several case reports describe corticosteroid abuse or dependence driven by the euphoria these medications can induce. These cases typically involve high-dose oral or intravenous formulations, but at least 1 case of dexamethasone nasal spray abuse has been reported.[33] Most cases of corticosteroid abuse have been described in patients with a premorbid history of either psychiatric illness or drug or alcohol dependence.[34]

MANAGEMENT

Management strategies for corticosteroid-induced psychiatric disturbances are based almost entirely on case reports, anecdotal evidence, and a few small case series. Understanding of this topic has grown only slightly during the past 50 years.

Several open-label studies have evaluated prophylactic regimens for prevention of adverse psychiatric effects associated with long-term corticosteroid treatment and reported successful use of lithium carbonate,[35] chlorpromazine,[36] valproic acid,[37] gabapentin,[38] and lamotrigine.[39] Falk et al[35] treated 27 patients empirically with lithium carbonate concurrent with corticotropin therapy for multiple sclerosis and retrobulbar neuritis. None of the 27 patients developed a psychotic reaction, whereas 6 (14%) of 44 retrospectively reviewed patients who received identical corticotropin therapy but no lithium carbonate developed psychosis.

Educating patients about potential adverse effects and asking about such effects at each patient encounter can enhance early intervention for adverse corticosteroid-induced psychiatric reactions. To illustrate this point, Reckart and Eisendrath[40] recruited 8 patients with chronic diseases at a university clinic to discuss their experience with corticosteroid adverse effects. Six of the 8 patients disclosed subtle but residual memory and cognitive difficulties. Only 1 of the 8 patients had been warned by a physician of possible behavioral or cognitive adverse effects, and 5 had not reported their psychiatric adverse effects to their physician for fear of being thought "insane." As with patients with mania and delirium, appropriate environmental and safety considerations must be addressed so that agitated patients do not have ready means to harm themselves or others. An overly stimulating environment can exacerbate a patient's condition.

Patients should be evaluated for any suggestion of suicidality.[41] Among patients with corticosteroid-induced psychosis, as many as 33% experience suicidal ideation.[42] Lewis and Smith[11] found that 2 of 79 patients with corticosteroid-induced severe mood disturbances completed suicide. Among 150 cases of corticosteroid-induced psychosis, Bräunig et al[42] found 26 patients with suicidality, including 15 with suicidal ideation, 8 who attempted suicide, and 3 who completed suicide.

Psychiatric disturbances that result from corticosteroid therapy commonly resolve slowly after discontinuation of the drug or reduction of the dosage.[43] Symptom duration is highly variable. Patients with delirium commonly recover in a few days, whereas those with psychosis generally take more than a week to return to baseline.[44,45] Depression, mania, or mixed affective states may take up to 6 weeks to resolve after discontinuation of the offending agent.

Initial treatment of corticosteroid-induced psychiatric disturbances should begin with cessation of the corticosteroids or reduction of the dosage. If cessation is not an option, the dosage should initially be tapered to 40-mg prednisone equivalents per day, followed by tapering to a physiologic dosage of 7.5-mg prednisone equivalents per day as quickly as is safe to do so.[46]

For patients who cannot tolerate corticosteroid cessation or dose reduction or who suddenly develop psychosis, severe agitation, aggressive behavior, or other intolerable symptom complexes, palliative pharmacotherapy is indicated, even though no definitive treatment has been identified. Myriad case reports have shown varying degrees of clinical success with mood stabilizers including lithium,[47-50] carbamazepine,[51] and valproic acid,[52,53] with selective serotonin reuptake inhibitors (SSRIs) including fluoxetine[54] and sertraline,[55,56] and with venlafaxine,[57] typical antipsychotics,[51,58,59] and atypical antipsychotics.[38,60-62]

The literature gives mixed reviews on the use of tricyclic antidepressants for the management of corticosteroid-induced psychiatric adverse effects. Some reports claim that doxepin[47,63] imipramine,[64] and amitriptyline[51] have helped to modulate mood. Others describe exacerbation of acute symptoms of agitation and psychosis with tricyclic antidepressants and recommend avoiding them.[51,63]

In a literature review specific to corticosteroid-induced psychosis, Davis et al[65] found that neuroleptics, generally in low doses, led to rapid symptom resolution in 24 (83%) of 29 patients. One third responded within 3 days, 60% within a week, and 80% within 2 weeks. Atypical antipsychotics cause far fewer dystonic reactions or other

extrapyramidal adverse effects than typical antipsychotics and are recommended as first-line treatment. In an open-label trial, Brown et al[62] recently found olanzapine to be effective in 11 (92%) of 12 outpatients being treated for corticosteroid-induced manic or mixed symptoms. Electroconvulsive therapy has proved useful in treating severe affective psychoses refractive to pharmacotherapy. In most such patients, symptoms have rapidly resolved after electroconvulsive therapy.[11,47]

Three case reports have described improvement of depressive symptoms with administration of SSRIs in patients receiving long-term corticosteroid therapy. Fluoxetine was prescribed in a case of active central nervous system Sjögren syndrome,[54] sertraline in a case of chronic hepatitis,[55] and sertraline in a child with a long-standing inflammatory condition.[56]

In summary, for acute corticosteroid-induced psychiatric disturbances, atypical antipsychotics generally appear to yield the greatest benefit with the fewest adverse effects. Antidepressants have been found to help in some situations but exacerbate agitation and psychosis in others. Limited data suggest a role for antidepressants in depressed patients who require long-term corticosteroid administration.

CORTICOSTEROID WITHDRAWAL

Although reduction or cessation of corticosteroids is the mainstay of treatment for corticosteroid-induced psychiatric reactions, caution is advised when making substantial or rapid reductions in corticosteroid doses, particularly for patients receiving long-term and high-dose treatments. For these patients, a taper is advised to prevent both physiologic and psychiatric corticosteroid withdrawal phenomena.[66] An inappropriate taper can result in 3 types of difficulties[67]: (1) suppression of the hypothalamic-pituitary-adrenal axis (HPA) with the potential for secondary adrenal insufficiency, (2) recurrence of the disease for which the therapy was initiated, and (3) a corticosteroid withdrawal syndrome characterized by symptoms of adrenal insufficiency but with normal HPA function. Appropriate tapering is critical and should be based on total dosage, therapy duration, and corticosteroid type.

Severe HPA suppression and corticosteroid withdrawal syndrome are both characterized by lethargy, malaise, depression, anorexia, nausea, myalgia, and arthralgias. When corticosteroids are stopped entirely, HPA suppression and corticosteroid withdrawal syndrome can be distinguished only by biochemical testing. In this instance, the corticotropin stimulation test is used to evaluate the integrity of the HPA.[67]

Corticosteroid withdrawal syndrome presents most commonly with depression, anxiety, and fatigue,[66] but mania[68] and delirium[69] have also been described. If patients develop intolerable withdrawal symptoms from a dose reduction, a temporary dose increase with a slower taper is advised. Symptoms of corticosteroid withdrawal syndrome generally resolve over 2 to 8 weeks.[11,43] A slower taper can be attempted after resolution of withdrawal symptoms.[68]

Recurrence of the underlying disease may necessitate resumption of corticosteroid therapy despite the psychiatric complications. The clinical scenario must dictate what is best for the patient, with careful consideration of the risks and benefits of corticosteroid treatment in light of these complications. Treatment recommendations are presented in Tables 3 and 4.

TABLE 3. **Treatment Algorithm for Patients Taking Short Courses (<1 mo) of Corticosteroids Who Develop Psychiatric Disturbances**

Evaluate for suicidal ideation or intractable agitation and consider hospitalization if either is present
Review medication profile for other potentially psychoactive medications and consider tapering or discontinuing if possible
If corticosteroids are suspected as causative, reduce dose as quickly as tolerated and physiologically prudent
If reaction is severe and/or does not respond to dose reduction, consider adding atypical antipsychotic medications

CONCLUSION

Corticosteroid-induced psychiatric disturbances are common and include mania, depression, psychotic or mixed affective states, cognitive deficits, and minor psychiatric disturbances (irritability, insomnia, anxiety, labile mood). In children, these effects commonly manifest as behavioral changes.

TABLE 4. **Treatment Algorithm for Patients Receiving Long-term Corticosteroid Therapy (>1 mo) Who Develop Psychiatric Disturbances**

Evaluate for suicidal ideation and consider hospitalization if it is present
Review medication profile for other potentially psychoactive medications and consider tapering or discontinuing if possible
Use lowest possible corticosteroid dose and discontinue corticosteroids as soon as possible, tapering as necessary to reduce risk of hypothalamic-pituitary-adrenal axis suppression
For ongoing affective symptoms, the following regimens may be tried
Manic symptoms
Mood stabilizer
Atypical antipsychotic
Depressive symptoms
Mood stabilizer
Selective serotonin reuptake inhibitor
Psychotic symptoms
Atypical antipsychotic

Which patients will experience corticosteroid-induced psychiatric disturbances cannot be predicted. Dosage is the most important risk factor for the development of adverse effects, with patients receiving less than 40 mg/d at minimal risk, those taking 40 to 80 mg/d at moderate risk, and patients receiving more than 80 mg/d at high risk. Most patients will develop symptoms during the first week of treatment, and more than 90% will develop symptoms by 6 weeks. Neither dosage nor any other identified factor predicts onset, duration, or severity of the psychiatric disturbance.

Most patients will recover fully with dose reduction or discontinuation of corticosteroid therapy. For those with symptoms of psychosis, aggression, or agitation, atypical antipsychotics should be first-line therapy, with expected responses within a week. Patients with persistent affective syndromes who are receiving long-term corticosteroid therapy should be maintained at the lowest effective corticosteroid dose and treated with an SSRI for depression and/or a mood stabilizer for mania or mixed states. All patients who develop psychiatric disturbances while taking corticosteroids should be evaluated for suicidal ideation at each physician encounter.

It is important that clinicians in all specialties become aware of the potential psychiatric adverse effects associated with corticosteroids and explain these effects to their patients. The accumulated literature on psychiatric reactions to corticosteroids is almost entirely composed of case reports and lacks scientific validation. Controlled studies are needed to further understand corticosteroid-induced psychiatric adverse effects.

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